Norbrook®

February 8, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Comments Concerning Docket No. 2004D-0468 - Draft Guidance For Industry 123: Target Animal Safety and Effectiveness Data to Support Approval of NSAIDs for Use in Animals

Dear Sirs:

Enclosed please find, in triplicate, comments that our company wishes to make concerning Docket No. 2004D-0468 - Draft Guidance For Industry 123: Target Animal Safety and Effectiveness Data to Support Approval of NSAIDs for Use in Animals.

We ask that you consider these comments as you finalize this draft guidance.

Regards,

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Director of Regulatory Affairs – USA & Canada

2004D-0468 C2

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Draft Guidance For Industry 123: Target Animal Safety and Effectiveness Data to Support Approval of NSAIDs for Use in Animals

Docket No. 2004D-0468

We wish to make the following comments concerning this draft guidance document:

I. INTRODUCTION.

Paragraph 1. Whilst it is true that NSAIDs can be renotoxic, and this may even be life threatening, the suggestion that "the toxicity of NSAIDs are frequently manifested in the.... .....renal system" is not borne out by experimental or pharmacovigilance data.

Paragraph 2. There are several lipoxygenases (spelling is incorrect, should be one "o"). Which does CVM have in mind? 5-LO?

II. DOSAGE CHARACTERIZATION

Paragraphs 2, 3, 4 and 5. This section discusses the concept of dose-response relationships and refers to dose titration studies. However, it goes on to say that dose optimization is no longer required following enactment of the ADAA. At the same time, it is recommended that sponsors are required to characterize the critical aspects of the dose-response relationship, but substantial evidence to characterize the critical aspects is not required. This guidance raises concerns. First, it is lacking in incisiveness. It leaves the sponsor in a state of uncertainty as to what the requirements of CVM are. Second, it might be considered very inadvisable to state that optimisation of dosage schedules is not required *for a class of drug which may have a narrow safety in general and a narrow safety margin in some individual animals in the treated population – arising from factors such as age, breed, pathophysiological state etc.* For such drugs optimisation of dosage is likely to be of particular significance. Third, the guidance fails to take account of the latest thinking in this area. By referring repeatedly to dose-titration studies (presumably carried out with either parallel or cross-over designs), the impression is created (by omission) that this is the CVM recommended route to dosage selection. In fact, in several publications, as summarised in recent reviews (Journal of Veterinary Pharmacology and Therapeutics – December 2004 issue) the latest thinking and best science in this area, as enunciated by Professors Landoni, Lees and Toutain, indicates that PK-PD modelling at molecular, clinical surrogate and clinical end-point levels can yield *in vivo* data on the three key pharmacodynamic parameters of the concentration-effect *(Note: NOT the dose-effect relationship)* relationship, namely efficacy (Emax), potency (IC_{50}, IC_{80}, IC_{90}, etc.) and sensitivity or slope (N). Moreover, PK-PD modelling studies take account of time (in addition to plasma concentration) as a second independent variable. By such modelling methods it is now possible to design dosage schedules to provide a given level of efficacy (based on plasma concentration rather than dose) with a low/acceptable level of toxicity and predictable level of efficacy. It may not be necessary to make PK-PD modelling a mandatory procedure but its advantages over and (on most counts) superiority to classical dose-titration studies should be mentioned, most especially as dose titration studies are specifically referred to. These

considerations apply to new animal drugs (novel molecule) but not necessarily to adequate characterisation of generic products or products containing an established drug in a new formulation.

Paragraph 4. Reference is made to well controlled studies but there is no indication of whether these should include positive or negative controls or both.

Paragraph 5. Reference is made to methods of determining dosage; suggested methods include "dose titration studies, pilot studies, *in vitro* studies and scientific literature". First, no mention is made of the important role of PK-PD modelling. Second, it is unclear what is meant by *in vitro* studies. Does CVM have in mind assays of potency for COX-1 and COX-2 inhibition? If so, is it recommended that assays be conducted using isolated enzymes, broken cells, cells in culture or whole blood assays?

III. TARGET ANIMAL SAFETY (TAS)

Paragraph 3. The usage of endoscopy to identify signs of gastrointestinal or renal toxicity will be very difficult to conduct. In addition, the possibility of causing trauma to the mucosa and inducing infection is greatly increased in the test animals. It is believed that these tests, without endoscopy, could be completed in laboratory animals to investigate the effect (toxicity) by post mortem and histopathology.

IV. FIELD STUDY

No comments.

V. USE OF PHARMACOKINETICS IN NSAID DEVELOPMENT

Paragraph 1. It would be helpful to expand the guidance on "mechanism of action". Presumably, quantitation at the molecular level of efficacy potency and sensitivity for inhibition of COX isoforms (COX-1 and COX-2) would be required for a new chemical entity (such evidence being already available for most existing drugs and therefore not necessary for generic products and those based on established actives). A second consideration is that the relationship between mechanism of action and dosages required for clinical use is scientifically interesting but complex, as discussed recently by Lees (2003, Immunopharmacology 11: 385-399).

Paragraph 2. It might be helpful to give more guidance on how pharmacokinetic data might be integrated or modelled (integration and modelling are not the same thing) with pharmacodynamic data in designing dose schedules for evaluation in clinical trials.

VI. LABELLING
A. General Approach to the Indication Section of Labelling - 1. Inflammation

Paragraph 3. The carrageenan sponge model has been used in laboratory animal (usually rat) studies and also in calves and horses. However, as it must be a requirement to develop models in the target species, CVM may wish to consider the extensively used tissue cage model as a preferential and better characterized alternative.

VI. LABELLING
A. General Approach to the Indication Section of Labelling – 2. Pain

Paragraphs 1, 2, 3, 4, 5, 6. The modality of pain is difficult to assess. Many means of assessment are subjective and require rigorous control of observer bias. It would be helpful for sponsors to have additional guidance on acceptable methods of pain assessment e.g. visual analogue scales, lameness scores, visual observation with semi-quantitative indices or more objective measures. Second, if NSAIDs are to be used to control post-operative pain, the timing of dosing may be crucial. For most NSAIDs it is likely that peak concentration in plasma and peak analgesia may be out of phase (hysteresis) by as much as 3 to 4 hours. The sponsor and regulator need therefore to consider whether dosing should be pre- or post-operative and whether an analgesic of another class (opioid ?) might be required in any interim period.

VI. LABELLING
C. Comparison of COX-1 and COX-2 Activity

Discouragement of the use of quantitative *in vitro* comparisons of COX-1 and COX-2 inhibitory activity is probably justified at the present time. However, as companies develop more selective products and demonstrate high selectivity for COX-2 inhibition *in well characterised whole blood assays*, say 100:1 or greater, this restriction may be less realistic. Moreover, the Guidelines might mention that there are *ex vivo* and *in vivo* methods for determining COX-1:COX-2 ratios of inhibition (see December 2004 issue of Journal of Veterinary Pharmacology and Therapeutics describing the work of Landoni and Lees), which might well be superior to existing *in vitro* studies.